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Citation for published version:
Dixon, JM, Rutgers, E & Hunt, KK 2014, 'Intraoperative assessment of axillary lymph nodes in patients with breast cancer', *British Medical Journal (BMJ)*, vol. 349, g6803. https://doi.org/10.1136/bmj.g6803

Digital Object Identifier (DOI):
10.1136/bmj.g6803

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
British Medical Journal (BMJ)

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Download date: 07. May. 2023

BMJ 2014;349:g6803 doi: 10.1136/bmj.g6803 (Published 25 November 2014)

EDITORIALS

Intraoperative assessment of axillary lymph nodes in patients with breast cancer

Time to abandon?

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The main advantage of intraoperative assessment of axillary lymph nodes in patients having surgery for breast cancer is that metastatic disease can be diagnosed and removed in a single operation. However, there are several disadvantages that have cast doubt on its use. These include concerns about its accuracy and the uncertainty that all patients with diseased sentinel nodes need additional treatment.

Accuracy questioned

Several methods have been used for intraoperative assessment of axillary nodes, including frozen section analysis, touch preparation cytology, and one step nucleic acid amplification. The National Institute for Health and Care Excellence (NICE) approved one step nucleic acid amplification in 2011, and it is the most widely used axillary staging method in the United Kingdom.[1]

A recent meta-analysis has raised doubts about the ability of one step nucleic acid amplification to accurately determine the extent of axillary node involvement.[2] The method is based on the measurement of messenger RNA for cytokeratin 19, expression levels of which vary between and within cancers, with copy numbers ranging from 4700 to 140 000 copies per microlitre. The meta-analysis concluded that the wide range of copy numbers in a fixed tumour volume precluded the accurate identification of macrometastases (≥2 mm) in lymph nodes.[2] The positive predictive value of one step nucleic acid amplification compared with histology was only 0.79, and the authors concluded that up to 21% of patients found to have positive lymph nodes using this method had micrometastases and therefore did not require axillary clearance. It is clearly time for NICE to re-evaluate its guidance on one step nucleic acid amplification.

Is treatment necessary?

Doubts that patients with positive nodes require additional treatment stem from a pivotal US trial with 25 year follow-up.[3] The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial found no survival benefit for patients with clinically node negative breast cancer who received axillary radiotherapy or axillary clearance compared with those whose nodes were treated only when they became palpable. More recently, the American College of Surgeons Oncology Group Z0011 trial evaluated axillary node dissection in clinically node negative patients having breast conserving surgery, whole breast radiotherapy, and adjuvant systemic treatment.[4] It compared the outcomes in patients with one or two positive sentinel nodes randomised to axillary lymph node dissection or sentinel lymph node biopsy alone. At median follow-up of 6.3 years there was no difference in the axillary recurrence rates between groups (0.5% versus 0.9%, respectively) and no improvement in survival with axillary lymph node dissection. Although this trial recruited fewer patients than originally planned, the findings were statistically valid.[4 5]The death rate was low in both arms of the trial, almost certainly because patients received effective systemic therapy, thus reducing the chances that axillary surgery could have influenced survival. Axillary lymph node dissection did, however, significantly increase the rate of lymphoedema.[5]

Two trials have since confirmed that patients with small volume axillary nodal disease do not require axillary lymph node dissection. The NSABP B-32 trial randomised 5600 patients with clinically node negative breast cancer to receive either axillary lymph node dissection or sentinel lymph node biopsy alone.[6] Over 4000 of the patients were pathologically node negative on haematoxylin and eosin staining, and immunohistochemistry identified axillary nodal micrometastases or isolated tumour cells in 616 of these patients. At 10 years there was no significant benefit in local control or overall survival in patients with micrometastases who had axillary clearance compared with those who had sentinel node biopsy alone. Similarly, a large randomised European trial found no benefits in disease control or survival for axillary node dissection compared with sentinel node biopsy alone in patients with micrometastases (<2 mm).[7] These and other studies led the

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American Society of Clinical Oncology to advise that patients with one to two positive nodes on biopsy who have breast conserving surgery, whole breast radiotherapy, and similar clinical and pathological characteristics to those enrolled in the Z0011 trial do not require routine axillary lymph node clearance.[8]

Alternative treatment

Axillary radiotherapy is an alternative to complete axillary lymph node dissection for patients with sentinel lymph node metastases. Studies performed 30 years ago compared axillary radiotherapy with axillary lymph node dissection and showed no difference in survival.[9 10]More recently, a large multicentre European study compared axillary radiotherapy with axillary lymph node dissection in patients with a positive sentinel node and showed no significant difference in the rates of axillary recurrence and survival.[11] However, the lymphoedema rate with axillary radiotherapy was half that seen in patients treated with lymph node dissection. Therefore, for women who are likely to benefit from axillary treatment, radiotherapy is a viable alternative to axillary dissection, offering similar rates of disease control but lower rates of morbidity.

Many centres in the United States have abandoned intraoperative assessment of sentinel nodes, but one step nucleic acid amplification continues to be widely used in the United Kingdom. Given the results from randomised trials, the guidelines from the American Society of Clinical Oncology, and the alternative options available for patients with diseased nodes, it seems unnecessary for patients to have intraoperative axillary lymph node assessment. It is imperative that decisions about how to treat axillary nodal disease are made with knowledge of tumour biology, the burden of disease in the sentinel nodes, and any planned radiotherapy and systemic therapy. Most importantly, patients need to participate in these decisions. Intraoperative frozen section analysis of breast tumours was abandoned long ago because it denied patients the opportunity to contribute to their treatment planning. It is now time to do the same with intraoperative sentinel lymph node assessment.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Cite this as: *BMJ* 2014;349:g6803

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